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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/645, 31/68, 31/405, 31/195 //</b> <b>(A61K 31/68, 31:645, 31:405, 31:195)</b> <b>(A61K 31/645, 31:405, 31:195)</b>	<b>A1</b>	<b>(11) International Publication Number: WO 96/11009</b> <b>(43) International Publication Date: 18 April 1996 (18.04.96)</b>
<b>(21) International Application Number:</b> PCT/GB95/02361 <b>(22) International Filing Date:</b> 5 October 1995 (05.10.95)  <b>(30) Priority Data:</b> 9420116.7                      5 October 1994 (05.10.94)                      GB 9508482.8                      26 April 1995 (26.04.95)                      GB  <b>(71)(72) Applicant and Inventor:</b> LODER, Cari [GB/GB]; 127 Russell Court, Woburn Place, London WC1H 0LP (GB).  <b>(74) Agents:</b> WILLIAMS, John, Francis et al.; Williams, Powell & Associates, 34 Tavistock Street, London WC2E 7PB (GB).	<b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> TREATMENT OF MULTIPLE SCLEROSIS (MS) AND OTHER DEMYELINATING CONDITIONS USING LOFEPRAMINE IN COMBINATION WITH L-PHENYLALANINE, TYROSINE OR TRYPTOPHAN AND POSSIBLY A VITAMIN B <sub>12</sub> COMPOUND		
<b>(57) Abstract</b>  The use of a combination of a tricyclic or tetracyclic antidepressant, a serotonin reuptake inhibitor, or a monoamine oxidase inhibitor with a neurotransmitter-inducing or precursor compound is proposed in the preparation of medication for the treatment or prevention of multiple sclerosis or other demyelinating conditions. For use in treatment to ameliorate the effects of a demyelinating condition, a daily regime is proposed of from 10 to 220 mg lofepramine and from 100 mg to 5 g of L-phenylalanine, optionally supplemented with injections of vitamin B <sub>12</sub> .		

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**TREATMENT OF MULTIPLE SCLEROSIS (MS) AND OTHER DEMYELINATING CONDITIONS USING LOFEPRAMINE IN COMBINATION WITH L-PHENYLALANINE, TYROSINE OR TRYPTOPHAN AND POSSIBLY A VITAMIN B<sub>12</sub> COMPOUND**

This invention relates to the treatment of Multiple Sclerosis (MS) and other Demyelinating Conditions.

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Multiple sclerosis is a common and well known neurological disorder. It is characterised by episodic patches of inflammation and demyelination which can occur anywhere in the central nervous system (CNS) almost always without any involvement of the peripheral nerves. The occurrence of the patches is  
10 disseminated in time and space, hence the older alternative name of disseminated sclerosis. It is believed that the pathogenesis involves local disruption of the blood brain barrier, a local immune and inflammatory response, with consequent damage to myelin and hence to neurons.

15 Clinically, MS can present in both sexes and at any age. However, its most common presentation is in relatively young adults, often with a single focal lesion such as damage to the optic nerve (optic neuritis), an area of anaesthesia or paraesthesia or muscular weakness. Vertigo, nystagmus double vision, pain, incontinence, cerebellar signs, L'Hermitte's sign (paraesthesia or pain in the arms  
20 and legs on flexing the neck) and a large variety of less common symptoms may occur. The initial attack is often transient and it may be weeks, months or years before a further attack occurs. Some fortunate individuals may have a stable condition, while other unfortunate ones may have an unrelenting downhill course ending in complete paralysis. More commonly there is a long series of remissions  
25 and relapses, each relapse leaving the patient somewhat worse than before. Relapses may be triggered by stressful events or viral infections. Elevated body temperature almost invariably makes the condition worse whereas a reduced temperature, for example induced by a cold bath, may make the condition better.

There are no satisfactory treatments for MS. Steroids may produce a temporary improvement but any beneficial effect invariably wears off. Recent clinical trials have shown that interferon may somewhat reduce the risk of relapse. However, the effect is modest and most patients still deteriorate.

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I have now developed a new and highly effective treatment for compensating for the effects of nerve damage caused by MS and other demyelinating conditions.

My invention is based on the use of a combination of an antidepressant or a mono-  
10 amine oxidase inhibitor in combination with an inducer or precursor of a neurotransmitter. The two compounds may be administered in the same dosage form, or may be in separate dosage forms but a combined pack may be in separate packs for administration at separate times but so as to be effective together in the body.

15

Lofepramine and related tricyclic and tetracyclic antidepressants work by interfering with the inactivation of substances called neurotransmitters which are required for the normal transmission of nerve impulses from one nerve cell to the next. Such neurotransmitters, among them substances called noradrenaline and serotonin, are  
20 released from one nerve cell and activate the next one. They are inactivated by various mechanisms including rapidly being taken up into nerve cells and also enzymic destruction by enzymes known as monoamine oxidase inhibitors (MAOI). Lofepramine is a drug which inhibits neurotransmitter uptake and which is in the class of tricyclic antidepressants and which also has some MAOI activity. Newer  
25 drugs to treat depression are more active against serotonin and are known as selective serotonin reuptake inhibitors (SSRIs).

I have discovered that the use of L-phenylalanine (LPA), the precursor of noradrenaline, contributes to the therapeutic effect. In some individuals, however,

an alternative may be L-tryptophan which is a precursor of the neurotransmitter, serotonin. Several different antidepressants including tricyclic antidepressants, SSRIs and MAOIs have beneficial effects but have consistently obtained the best results with lofepramine. Detailed information on lofepramine is given in the  
5 Merck Index. I have also noted that when the patient receives regular injections of vitamin B<sub>12</sub> the treatment works best.

- As an example, a regime of 70 mg lofepramine and 500 mg LPA per day for over a year in my own case completely resolved severe unequivocally diagnosed MS.
- 10 Over 100 other patients have done well on a similar regime, although some have been given other antidepressants either of the traditional tricyclic class, such as amitriptyline or imipramine, or the newer specialist serotonin uptake inhibitors or monoamine oxidase inhibitors. Four particular instances are given in the appendix. Most have done best on lofepramine. The doses of LPA have also varied from  
15 about 100 mg to up to 5 g per day, but best results are obtained with doses in the region of 500-2000 mg/day. The doses of antidepressants (with the proviso that minimum effective and maximum safe levels are determined according to the drug), lie broadly in the range 10 mg to 200 mg per day.
- 20 A background course of vitamin B<sub>12</sub> for example by injection, is also preferred and does have a beneficial effect. Daily amounts may for example be the conventional daily requirement for the vitamin.

Four case histories of patients other than myself illustrating the beneficial effects of  
25 my invention are given later herein. A total of 126 patients have now been tested and almost all have received benefit. This benefit has reached varying degrees with some only showing a small improvement and others a complete resolution of all symptoms such as I observed in myself.

### Treatment Examples

- A specific example of the use of the treatment is 70 mgs (half the therapeutic starting dose for depression) of lofepramine taken each morning with 500 mgs of L-phenylalanine, and 500 mgs of L-phenylalanine taken mid afternoon. For patients with the regular MS attacks of chronic progressive MS it is desirable to include an 8 -10 week course of 1000 micrograms of hydroxocobalamin (intra muscular) per week at the start of treatment and then 1000 micrograms every ten days thereafter.
- 10 Other TCADs or MAOIs may be substituted for lofepramine and higher doses of antidepressants, L-phenylalanine may be indicated in individuals who fail to respond to the suggested levels. It is not advised to exceed the usual maximum prescribing dose of lofepramine (or another TCAD or MAOI) but doses between 70 mg and 210 mg of lofepramine can be prescribed. The doses of L-phenylalanine can then be increased in proportion to the dose of the TCAD or MAOI.

For instance:        70 mg lofepramine + 500 mg L-phenylalanine twice per day.  
                         120 mg lofepramine + 1000 mg L-phenylalanine twice per day.  
                         210 mg lofepramine + 1500 mg L-phenylalanine twice per day.

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This drug treatment is not appropriate for individuals with a history of cardiac problems, high blood pressure or for those suffering from PKU.

### Composition Examples

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1. Tablets of 500 mg L-tryptophan, or L-phenylalanine or the two combined to be taken at a dose of 1-10/day in accordance with an appropriate daily dose of an antidepressant chosen from the classes of tricyclic or tetracyclic antidepressants, monoamine oxidase inhibitors or serotonin reuptake

inhibitors. Examples of such drugs and some typical doses per day include lofepramine (70 mg), imipramine (100 mg), clomipramine (50 mg), amitriptyline (150 mg), nortriptyline (75 mg), mianserin, protriptyline (40 mg), venlafaxine, fluvoxamine (150 mg), fluoxetine (20 mg), maprotiline (75 mg), sertraline, pargyline, mocloperamide, triazolopyridine, phenelzine (45 mg), tranylcypromine (20 mg), desipramine, dothiepin (70 mg), doxepin (100 mg), paroxetine, trimipramine, oxazine or viloxazine (500 mg). However, any other member of these classes of drugs not listed here may be used in this way, in doses indicated in standard texts.

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2. Tablets as in (1) in which an appropriate dose of the amino acid is combined with an appropriate dose of the chosen antidepressant in the same dosage form so that an adequate daily dose of each can be provided.
- 15 3. Tablets containing 25-100 mg of lofepramine, together with 500 mg of phenylalanine, or 500 mg of tryptophan, or 250 mg of each. Normally such tablets would be used so as to provide a daily dose of 50-200 mg lofepramine together with 500-1000 mg of the amino acids.
- 20 4-6 Other appropriate dosage forms for 1-3 such as soft or hard gelatin capsules, emulsions, creams, whips, solutions, or any dosage form known to those skilled in the art.

Case Histories

- 5 Patient A 49y female. MS for 20 years. Symptoms on starting treatment: weak legs; rapid fatigue on exercise; bladder urgency and frequency with incontinence; arms too weak to allow self dressing; right hip pain. After 12 weeks treatment: complete disappearance of all symptoms.
- 10 Patient B 45y male. MS for 12 years. Symptoms on starting treatment: confined to wheelchair; legs spastic and weak; arms weak and rapidly fatigued; hands numb; bladder urgency and incontinence. After 8 weeks treatment: fatigue and weakness of arms and legs greatly improved; spasticity less; bladder improved; walking on crutches instead of wheelchair.
- 15 Patient C 38y male. MS for 2 years. Symptoms on starting treatment: badly slurred speech; fatigue; bladder urgency and frequency; limited to half a mile walking even with a stick; poor hand control and writing. After 6 weeks treatment: fatigue better; speech much less slurred; eyesight and writing improved; can walk half a mile without a stick.
- 20 Patient D 40y female. MS for 3 years. Symptoms on starting treatment: poor balance; optic neuritis; spasticity and spasms with pain in legs and feet; bladder urgency; "shimmering" sight. After 3 weeks treatment: spasms, spasticity and pain completely relieved; bladder function better; balance better; "shimmering" sensation disappeared.
- 25



CLAIMS

1. The use of a combination of a tricyclic antidepressant or a monoamine oxidase inhibitor with a neurotransmitter-inducing compound in the preparation of medication for the treatment of multiple sclerosis or other demyelinating conditions.
2. The use of a combination of a tricyclic or tetracyclic antidepressant, a serotonin reuptake inhibitor, or a monoamine oxidase inhibitor with a neurotransmitter-inducing or precursor compound in the preparation of medication for the treatment or prevention of multiple sclerosis or other demyelinating conditions.
3. Use according to claim 1 or 2, in which the inducing compound is an amino acid, particularly L-phenylalanine, tyrosine, or tryptophan.
4. Use according to claim 1, 2, or 3, in which the antidepressant is lofepramine.
5. Use according to any of claims 1 to 4, in which the two drugs are administered together daily followed by a further daily dose of the inducing compound.
6. A method of treatment or prevention of nerve damage caused by multiple sclerosis and other demyelinating conditions e.g. encephalomyelitis. which comprises administering a combination of a tricyclic or tetracyclic antidepressant or a monoamine oxidase inhibitor and a neurotransmitter-inducer e.g. L-phenylalanine, tyrosine or tryptophan.
7. A method according to claim 6 supplemented with treatment with cyanocobalamin or hydroxocobalamin.

8. A combination of a tricyclic antidepressant or a monoamine oxidase inhibitor, with a neurotransmitter-inducing compound.
9. A combination of a tricyclic antidepressant or a monoamine oxidase inhibitor, with a neurotransmitter-inducing compound and cyanocobalamin or hydroxocobalamin.
10. A composition of an antidepressant drug and an amino acid, as above, optionally together with vitamin B<sub>12</sub> through the  $\alpha$ -amino group cobalt atom.
11. A method of treating or preventing MS by co-administering an antidepressant drug, selected from the classes of tricyclic or tetracyclic antidepressants, serotonin reuptake inhibitors and monoamine oxidase inhibitors, together with a neurotransmitter precursor.
12. A method of preparation of a medicament for treating or preventing MS wherein use is made of an antidepressant drug together with a neurotransmitter inducer or precursor compound or of either of them alone when the medicament is for administration with the other.
13. A method as in claim 11 in which the antidepressant drug is lofepramine.
14. A method as in claim 11 or 12 using vitamin B<sub>12</sub> administered for example orally or, preferably, by injection.
15. A method as in claim 11 or 12 in which the neurotransmitter precursor is L-phenylalanine.

16. A method as in claim 11 or 12 in which the neurotransmitter inducer or precursor is L-tryptophan.
17. A method as in claim 11 or 12 in which both L-phenylalanine or tyrosine and L-tryptophan are used with the antidepressant.
18. For use in treatment to ameliorate the effects of a demyelinating condition, a daily regime of from 10 to 220 mg lofepramine and from 100 mg to 5g of L-phenylalanine, optionally supplemented with injections of vitamin B<sub>12</sub>.
19. For use in treatment to ameliorate the effects of a demyelinating condition, a daily regime of from 70 to 210 mg lofepramine and from 500 mg to 3000 mg of L-phenylalanine, optionally supplemented with injections of vitamin B<sub>12</sub>.
20. A unit dosage form containing lofepramine (25-100 mg) and L-phenylalanine (400-600 mg).

## INTERNATIONAL SEARCH REPORT

 Internat. Application No  
 PCT/GB 95/02361

## A. CLASSIFICATION OF SUBJECT MATTER

 IPC 6 A61K31/645 A61K31/68 A61K31/405 A61K31/195 //(A61K31/68,  
 31:645,31:405,31:195), (A61K31/645,31:405,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. IMMUNOPHARMACOL., vol. 4, no. 3, 1983 pages 153-162, C.F. SCOTT ET AL. 'Experimental allergic encephalitis; treatment with drugs which alter CNS serotonin levels'	1-3,6,8, 10-12,16
Y	see the whole document ---	1-20
X	GB,A,2 082 910 (BERK PHARMACEUTICALS LTD) 17 March 1982	8,10
Y	see the whole document ---	1-20
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search

11 March 1996

Date of mailing of the international search report

22.03.96

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## INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/GB 95/02361

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. NEUROL. SCI., vol. 35, no. 1, 1978 pages 157-166, D. CHADWICK ET AL. '5-Hydroxytryptophan-induced myoclonus in Guinea pigs'	8,10
Y	see page 157 see page 163 ---	9
X	NEUROSCI. LETT., vol. 141, no. 1, 1992 pages 35-38, K.N. WESTLUND 'Serotonin is found in myelinated axons of the dorsolateral funiculus in monkeys'	8,10
Y	see abstract see page 37 ---	9,10
Y	DE,A,35 19 687 (AREND VEIT;HOETING HANS; DIEHL IWAN DR MED) 4 December 1986 see the whole document ---	1-15, 17-20
Y	US,A,4 409 243 (LIEB JULIAN) 11 October 1983 see the whole document ---	1-20
Y	DE,A,26 28 558 (LEO AB) 20 January 1977 see the whole document ---	1-20
Y	US,A,4 650 789 (POLLACK ROBERT L) 17 March 1987 see the whole document see column 7 ---	1-20
Y	J. NEUROIMMUNOL., vol. 40, no. 2-3, 1992 pages 225-230, E.H. REYNOLDS 'Multiple sclerosis and vitamin B12 metabolism' see the whole document ---	7,9,10, 14,18,19
Y	DE,A,42 04 102 (KRAGLER PETER) 19 August 1993 see the whole document ---	7,9,10, 14,18,19
A	BIOCHEM. PHARMACOL., vol. 42, no. 4, 1991 pages 921-929, A. BADAWY ET AL. 'The effects of lofepramine and desmethylinipramine on tryptophan metabolism and disposition in the rat' see the whole document ---	1-20
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## INTERNATIONAL SEARCH REPORT

Internat Application No  
PCT/GB 95/02361

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PAYKEL, E.S. (ED.) 'Handbook of affective disorders' 1992, GUILFORD PRESS, NEW YORK, USA Goodwin G.M.: Tricyclic and newer antidepressants see page 327 - page 343 see page 339 -----</p>	1-20

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB95/02361

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 6,7,11,13-17 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-17  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Please see annex!
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Expressions like "tricyclic antidepressant", "tetracyclic antidepressant", "monoamine oxidase inhibitor", "neurotransmitter-inducing or precursor compound" etc. are not sufficient to characterize specific compounds and do not allow a complete search. The search has therefore been restricted to the compounds explicitly mentioned in the claims and to the general inventive concept.

Claims searched completely: 18-20  
Claims searched incompletely: 1-17



# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. Application No

PCT/GB 95/02361

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2082910	17-03-82	NONE	
DE-A-3519687	04-12-86	NONE	
US-A-4409243	11-10-83	US-A- 4490385	25-12-84
DE-A-2628558	20-01-77	GB-A- 1497306	05-01-78
		BE-A- 843691	03-01-77
		CA-A- 1079274	10-06-80
		CH-A- 618686	15-08-80
		FR-A,B 2316234	28-01-77
		JP-C- 1293131	16-12-85
		JP-A- 52007982	21-01-77
		JP-B- 60014030	11-04-85
		SE-A- 7607565	04-01-77
		US-A- 4172074	23-10-79
US-A-4650789	17-03-87	US-A- 4853377	01-08-89
DE-A-4204102	19-08-93	NONE	